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# Association of passive smoking with increased coronary heart disease risk is not explained by elevation of leucocyte count

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**The increased risk of coronary heart disease in cigarette smokers may be due at least partly to an elevation of the leucocyte count. Chronic passive smoking has also been found to be associated with an increased risk of coronary heart disease, but its effect on the leucocyte count has not been reported. In this study 250 male factory employees aged 20–64 years were interviewed on smoking behaviour and exposure to environmental tobacco smoke, and blood counts were determined. Urinary cotinine was measure by radio-immunoassay and corrected for urinary creatinine concentrations. Mean leucocyte count was significantly higher among smokers compared with non-smokers (8,666 compared to 6,900; p<0.001). On the basis of smoking history, passive smokers had leucocyte counts similar to non-smokers. These findings were confirmed when leucocyte counts were compared with urine cotinine to creatinine ratios. The association of haematocrit and haemoglobin with smoking was similar to that of leucocyte count. These findings suggest that any association of passive smoking with coronary heart disease is not through an elevation of leucocyte count.**

Key words: smoking, passive smoking, urine cotinine, blood count, leucocytes, coronary heart disease

Leucocyte count has been shown to be independently associated with an increased risk of coronary heart disease (Friedman et al. 1974, Zalokar et al. 1981, Kostis et al. 1984, Ernst et al. 1987). In addition, cigarette smokers tend to have higher leucocyte counts than non-smokers (Petitti & Kipp 1986, Green et al. 1992) and it has been suggested that this may be one of the mechanisms by which smoking increases the risk of coronary heart disease (Kostis et al. 1984, Ernst et al. 1987). Exposure to environmental tobacco smoke (passive smoking) has also been shown to be associated with coronary heart disease (Garland et al. 1985, Glantz & Parmley 1991), although the mechanism of this association is not clear. Toxic agents have been demonstrated in both mainstream cigarette smoke (smoke inhaled and exhaled by the smoker) and side-stream cigarette smoke (emitted from the burning zone) (Hoffman & Hoffman 1987, Erikson et al. 1988). There is some evidence that enzyme systems responsible for the detoxification of smoke constituents are not induced to the same extent in passive smokers as in active smokers (Hoffman & Hoffman 1987, Erikson et al. 1988). In a recent study, three hours of heavy exposure of 16 non-smokers to environmental tobacco smoke produced a mean increase of 33 per cent in leucocyte count (Anderson et al. 1991). However, to the best of our knowledge there are no reports on whether chronic passive exposure to environmental tobacco smoke is reflected in an elevation of the leucocyte count.

Self-reported exposure to environmental tobacco smoke may only be a crude estimate of actual exposure. Since nicotine in the blood has a short half-life of about two hours (Curvall et al. 1990) it is not suitable as a measure of chronic exposure. On the other hand, cotinine, the major metabolite of nicotine, is specific to tobacco and is concentrated and excreted in the urine and saliva (Curvall et al. 1990). It has a half-life of about 19 hours in the blood and it has been shown that the urinary cotinine level is a sensitive measure of daily exposure to tobacco smoke (Wald et al. 1984, Wall et al. 1988, Cummings et al. 1990).

The aim of this study was to compare the leucocyte count in cigarette smokers with that of non-smokers exposed to varying concentrations of environmental tobacco smoke. Urinary cotinine concentrations were used to determine the extent of exposure to environmental tobacco smoke. While the emphasis in this study was to evaluate the association of exposure to tobacco smoke and leucocyte count, haematocrit per cent and haemoglobin concentration are also analyzed for the sake of comparison.

## METHODS

### *Subjects*

Three hundred seventy-five men aged 20–64 and employed in a single industrial worksite (93% were blue-collar workers), underwent routine health screening carried out by staff from our institute. Participation was voluntary and the examinations were offered free of charge. The response rate for participation in the study was almost 100

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per cent. A random sample of 250 were included in a special study of passive smoking. The subjects were all interviewed by the same trained interviewer, using a questionnaire on current smoking habits, exposure to tobacco in the workplace and exposure to tobacco smoke at home. A typical question was structured as follows: Do your co-workers smoke in your work area? 1) Not at all; 2) Infrequently; 3) Frequently; 4) Most of the time. Answers 2, 3 and 4 correspond to the classification of mild, moderate and extensive exposure to tobacco smoke. Four groups were defined: a) Active smokers (categorized by <10, 10–20 and >20 cigarettes per day); b) non-smokers reporting minimal exposure to tobacco smoke both in the workplace and at home; c) non-smokers reporting moderate exposure to tobacco smoke of others in the workplace or at home; and d) non-smokers reporting extensive exposure to tobacco smoke of others in the workplace or at home. Subjects were asked to provide urine samples during a regular workday, between 12:00 p.m. and 2:00 p.m. Aliquots of 1.8 ml were kept in serum storage tubes (screw top) at −70°C until tested.

*Urinary cotinine and creatinine measurements*

Urinary cotinine concentrations were determined in the nephrology research laboratory at Meir General Hospital, using radio-immunoassay (RIA) (Double Antibody Nicotine Metabolite, Diagnostic Products Corporation, Los Angeles). Quality control was monitored by means of control standards which were included with the test kit and control urines which were stored at −20°C. Since it was not possible to obtain 24-hour urine samples, urinary creatinine was determined using standard methods on an automatic analyzer in order to correct for the cotinine concentrations in random urine specimens. The cotinine results (in ng/ml) were expressed relative to the urinary creatinine concentrations (mg/dl), a method used successfully by other investigators (Wall et al. 1988, Cummings et al. 1990).

*Statistical analyses*

The mean cotinine concentrations, cotinine to creatinine ratios and blood counts for each of the subgroups identified by the questionnaire were compared by one-way analysis of variance and Duncan's multiple range test. The mean blood counts were compared graphically for different intervals of cotinine:creatinine ratios and tested for trend by means of linear regression. In addition, the association between blood counts and the cotinine creatinine ratios were examined using non-linear regression.

## RESULTS

Some degree of passive exposure to tobacco smoke at work was reported by 85.6 per cent, whereas only 27.3 per cent reported any such exposure at home. Urinary cotinine concentrations and cotinine to creatinine ratios are shown by smoking status in *table 1*. The cotinine creatinine ratios distinguish between four distinct groups based on self-reported exposure to tobacco smoke: minimal or moderate passive exposure, heavy passive exposure or smoking less than 10 cigarettes per day, smoking 10–20 cigarettes per day, and smoking more than 20 cigarettes per day. Nevertheless, there was overlapping of the ranges of cotinine to creatinine ratios between the self-reported categories, suggesting either in-accuracy of self-reporting, or variation in nicotine absorption or metabolism, or both. Results for the comparison of the blood parameters in the different sub-groups classified by reported smoking or exposure to tobacco smoke are shown in *table 2*. Those smoking more than 10 cigarettes per day had a significantly higher mean leucocyte count than the light smokers or non-smokers regardless of the degree of passive exposure to tobacco smoke. Haematocrit and haemoglobin showed a similar pattern.

The mean blood counts by different intervals of the cotinine to creatinine ratio are shown in the *figure*. While the linear trends were significant in all three, the counts were clearly elevated only at levels of the cotinine to creatinine ratio consistent with heavy smokers and much higher than those seen in non-smokers exposed to envi-

**Table 1** Mean (± standard deviation) urinary cotinine and cotinine:creatinine ratios, by smoking status (minimum and maximum given in parentheses)

| | | Urinary markers | | | | | |
|---|---|---|---|---|---|---|---|
| | | Cotinine concentration (ng/ml) | | | Cotinine:creatinine ratio | | |
| Smoking status | n | Mean | SD | Range | Mean | SD | Range |
| Non-smokers | | | | | | | |
| None or minimal passive exposure | 60 | 36.3[a] | 36.2 | 0–175 | 0.3[a] | 0.3 | 0–1.2 |
| Moderate passive exposure | 64 | 154.3[a] | 473.2 | 0–2,644 | 0.9[a] | 2.7 | 0–14.2 |
| Heavy passive exposure | 22 | 1,074.1[b] | 2,745.7 | 0–10,593 | 10.4[b] | 25.8 | 0–93.7 |
| Smokers | | | | | | | |
| < 10 cigarettes per day | 27 | 2,100.8[b] | 2,327.6 | 45–8,522 | 12.9[b] | 11.6 | 0.5–42.2 |
| 11–20 cigarettes per day | 42 | 7,242.3[c] | 5,277.7 | 458–22,299 | 38.1[c] | 20.1 | 2.7–90.3 |
| ≥ 20 cigarettes per day | 35 | 7,853.3[c] | 3,864.4 | 85–22,036 | 44.6[d] | 16.9 | 0.6–82.6 |
| $F_{3,29}$ (one-way analysis of variance) | | 65.7 | | | 85.9 | | |
| P | | < 0.0001 | | | < 0.0001 | | |

[a], [b], [c], [d] indicate significantly different groups by Duncan's multiple range test at the 5 per cent level of significance.



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Table 2 Mean leucocyte count, haematocrit and haemoglobin by smoking status (95% confidence interval in parentheses)

| Smoking status | n | Blood parameters: Leucocyte count (x1,000) | | Haematocrit | | Haemoglobin (g/100 ml) | |
|---|---|---|---|---|---|---|---|
| Non-smokers | | | | | | | |
| None or minimal passive exposure | 60 | 6.90 | (6.52-7.23)[a] | 43.6 | (42.9-44.3)[a] | 14.6 | (14.4-14.8)[a] |
| Moderate passive exposure | 64 | 7.03 | (6.64-7.41)[a] | 43.1 | (42.6-43.5)[a] | 14.4 | (14.2-14.5)[a] |
| Heavy passive exposure | 22 | 6.76 | (6.15-7.36)[a] | 43.4 | (42.3-44.5)[a] | 14.5 | (14.0-14.9)[a] |
| Smokers | | | | | | | |
| < 10 cigarettes per day | 27 | 7.13 | (6.66-7.66)[a] | 43.4 | (42.5-44.2)[a] | 14.5 | (14.2-14.8)[a] |
| 11-20 cigarettes per day | 42 | 8.00 | (7.34-8.63)[b] | 44.5 | (43.7-45.2)[b] | 14.9 | (14.6-15.2)[b] |
| ≥ 20 cigarettes per day | 35 | 8.66 | (8.01-9.24)[b] | 44.5 | (43.8-45.8)[b] | 15.0 | (14.7-15.4)[b] |
| F-ratio (one-way analysis of variance) | | 7.8 | | 3.2 | | 3.4 | |
| P | | < 0.001 | | 0.009 | | 0.005 | |

[a,b] Indicate significantly different groups by Duncan's multiple range test at the 5 per cent level of significance

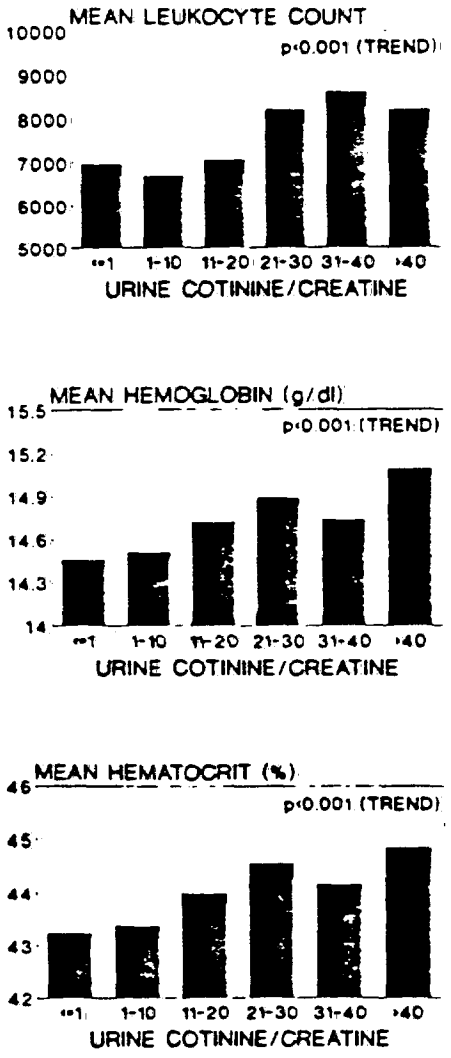


Figure Mean leukocyte count, hematocrit ratio and hemoglobin by intervals of the urinary cotinine to creatinine ratio

ronmental smoke. Non-linear regression of the blood counts on the cotinine to creatinine ratio yielded a highly significant second degree polynomial term, confirming this observation (detailed analyses not shown).

## DISCUSSION

These findings demonstrate that leucocyte count is not significantly elevated in non-smokers exposed to different levels of environmental tobacco smoke. In addition, among light smokers there was no increase in leucocyte count. This suggests that if in fact elevation of the leucocyte count contributes to the risk of coronary heart disease in smokers, this is not likely to be the mechanism for passive smokers or indeed for light smokers. In general the mechanism for the increased risk of coronary heart disease in passive smokers is not well understood. It has been postulated that it may be due to effects on blood factors such as platelet aggregation or through a role of the damaging and mutagenic effects of agents such as the polycyclic aromatic hydrocarbons (PAH) on the endothelial and smooth muscle cells (Glantz & Parmley 1991). In addition, extensive exposure to environmental tobacco smoke may result in reduced oxygen supply to the myocardium (Glantz & Parmley 1991).

It has been suggested that the elevation of the white cell count in smokers results from a chronic inflammatory response in the bronchi of regular smokers (Petitti & Kipp 1986). Toxic products in cigarette smoke such as tar and cadmium may be responsible for this effect (Lewis et al. 1972). Despite the fact that cigarette smoking has an acute effect on the leucocyte count (Friedman et al. 1973), this effect persists for some time after quitting (Petitti et al. 1986). This may be due at least in part to changes in hormonal levels resulting from smoking which in turn might affect the leucocyte count (Petitti & Kipp 1986).

The findings in this study suggest that at the population level, at least among adult men, chronic exposure to environmental tobacco smoke has little or no effect on leucocyte count. The relatively narrow confidence intervals for the leucocyte counts suggest that even if the study



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was performed on a larger sample, the results would be largely unchanged. Despite this finding, an effect in some heavily exposed individuals cannot be excluded. It should be mentioned that most of the subjects were blue-collar workers, although there is no obvious reason to predict different findings for white-collar workers. The possibility that passive smoking may have some effect on subfractions of leucocytes cannot be excluded (Anderson et al. 1991). Nevertheless, the results of the present study indicate that the mechanism underlying the increased risk of coronary heart disease in passive smokers is not through elevation of leucocyte count.

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